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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/627,485	07/25/2003	Zejun Xiao	X-0231	4226

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EXAMINER	
NWAONICHA, CHUKWUMA O	
ART UNIT	**PAPER NUMBER**
1621	

DATE MAILED: 07/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/627,485	XIAO ET AL.	
	Examiner	Art Unit	
	Chukwuma O. Nwaonicha	1621	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on 7/25/03.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim 1 is pending in the application.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119 (e) is acknowledged.

Specification

The structure of folic acid is objected to because of the carbonyl carbon has five bonds while nitrogen has two bonds (page 2 of specification). Corrections are required. The reference Harris et al in 1990 is wrongly cited (page 5 of specification). The U.S. patent number is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

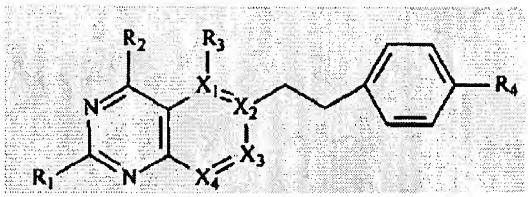
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hausheer et al. {WO 98/24789}, and further in view of Nair {U.S. Pat. 5,912,251}.

Applicants' claim a process for synthesizing compounds having the formula: I as shown below:



wherein R_1 and R_2 are each individually amino or N-alkyl substituted amino; hydroxy; alkoxy; keto; lower alkyl; or a nitrogen or oxygen protecting group;

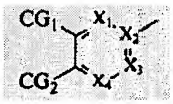
R_3 is hydrogen; hydroxy; alkoxy; trifluoromethyl alkoxy; halo; sulfhydryl or alkylthio;

R_4 is hydroxy; alkoxy; or --C(O)--X;

X is hydroxy; alkoxy; or an amino acid residue;

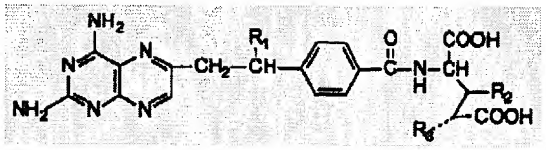
X_1, X_2, X_1 and X_4 are each individually carbon or nitrogen.

The applicants' teaching involves a process comprising the steps of: (a) providing the starting compound of the formula:



Wherein CG_1 and CG_2 are moieties amenable to an annulation reaction, (b) annulation the starting compound to form a 1N, 3N two-ring fused heterocycle, (C) derivatizing the two-ring fused heterocycle at the 6-position to form an intermediate, and (d) adding a derivative of *p*-benzoic acid to the intermediate to form the desired product.

Hausheer et al. disclose a process for synthesizing a compound of the formula:



wherein R_1 is hydrogen, R_2 is hydrogen, R_3 is methylene and the dashed line indicates a double bond; said process comprising the steps of (a) providing the starting reagent 2,4,5,6-tetraamino pyrimidine, (b) reacting the starting reagent with 1,3-dihydroxy-2-propanone to form the intermediate compound, 6-hydroxylmethyl pteridine, (c) reacting the intermediate compound with brominating reagent to form 6-bromomethyl pteridine, alkylating the 6-bromomethyl pteridine to form an esterified intermediate, (e) hydrolyzing the esterified intermediate compound to form the acid homologue, (f) reaction the acid homologue with a γ–methylene glutamate eater to produce an esterified form of the desired and (g) hydrolyzing the esterified compound to give the desired antifolate compound, (see pages 2 and 21-24 of WO 98/24789).

The difference between the applicants' claimed invention and Hausheer et al. is that applicants' use a different starting material (5-methyl-2-nitrobenzoic acid) to produce the corresponding amide and its subsequence transformation to 5-methyl-2-nitrobenzonitrile, (pages 10-11 of the specification) while Hausheer et al. employes 2,4,5,6-tetraamino pyrimidine as their starting reagent.

However, Nair teach a process for preparing antifolates by using commercially available 5-methyl-2-nitrobenzoic acid as a starting material to produce the corresponding amide and its subsequence transformation to 5-methyl-2-nitrobenzonitrile, (see U.S. page 4 lines 1-60 of Pat. 5,912,251).

It would have been *prima facie* obvious to one of ordinary skill in the art, in view of Hausheer et al. and Nair to make an antifolate compounds via the presently claim process because Hausheer et al. and Nair teach that the presently claimed process can be used to produced antifolates.

One of ordinary skill in the art would have been motivated, in view of Hausheer et al. and Nair to make antifolate compounds through the claim process by alternating/varying the synthetic steps to arrive at the desired compound in order to achieve a desired goal, for example: higher product yield, higher purity or low production cost. The instantly claimed process would therefore have been obvious to one of ordinary skill in the art.

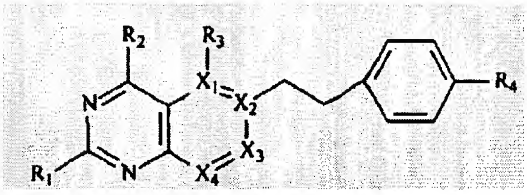
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 is rejected under 35 U.S.C. 102(b) as being clearly anticipated by Nair {U.S. Pat. 5,912,251}.

Applicants' claim a process for producing compounds having the formula: I as shown below:



I

wherein R_1 and R_2 are each individually amino group;

R_3 is hydrogen;

R_4 is -C(O)--X;

X is an amino acid residue;

X_1, X_2, X_1 and X_4 are each individually carbon.

The applicants' claim process for the preparation of antifolates comprising the steps of: (a) providing the starting compound (5-methyl-2-nitrobenzoic acid, page 10 of the specification), (b) annulation the starting compound to form a 1N, 3N two-ring fused heterocycle, (C) derivatizing the two-ring fused heterocycle at the 6-position to form an intermediate, and (d) adding a derivative of *p*-benzoic acid to the intermediate to form the desired product.

Nair teach a process for preparing an antifolate compound of general formula I by conversion a commercially available 5-methyl-2-nitrobenzoic acid to the corresponding amide and its subsequence transformation to 5-methyl-2-nitrobenzonitrile. The resulting intermediate is then reacted with p-formymethylbenzoate to provide an olefin compound. Reduction of the olefin compound with sodium dithionite gave the aminonitrile which was cyclized with guanidine to the corresponding pteroate analogue which after catalytic hydrogenation and hydrolysis gave 4-amino-4-deoxy-5,8,10-trideazapteroic acid. The coupling of 4-amino-4-deoxy-5,8,10-trideazapteroic acid with diethyl-4-methyleneglutamate followed by mild

hydrolysis of the resultant diester gave the desired antifolate product, (see U.S. page 4 lines 1-60 of Pat. 5,912,251).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chukwuma O. Nwaonicha whose telephone number is 571-272-2908. The examiner can normally be reached on Monday thru Friday, 8:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chukwuma O. Nwaonicha, Ph.D.
Patent Examiner
Art Unit: 1621

J. PARSA
PRIMARY EXAMINER

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